REMARKS

Applicants respectfully request reconsideration of the Office Action mailed on May 6, 2008 and allowance of the claims.

The rejection states claims 15, 18, 20-22 and 27-30 are pending and claims 28-29 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b) as being directed to non-elected subject matter.

Applicants thank the Examiner for the explanation regarding the status of claims 28-29 and 15-18 (a result of the restriction and election of species).

Claims 15, 18, 20-22 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid (compound of claim 18 and 27 and encompassed by the generic formula of claim 15), does not reasonably provide enablement for the use of the same. The rejection states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The rejection states in this regard, the application and disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1. the nature of the invention;
2. the breadth of the claims;
3. the predictability or unpredictability of the art;
4. the amount of direction or guidance presented;
5. the presence or absence of working examples;
6. the quantity of experimentation necessary;
7. the state of the prior art; and
8. the relative skill of those skilled in the art.

The rejection states that the relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The rejection states that the presently claimed invention is directed to a compound of formula (Ib) (instant claim 15), specifically, the elected compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid (instant claims 18 and 27), and a pharmaceutical composition thereof that further comprises one or more pharmaceutically acceptable excipients, diluents or carriers (instant claim 20). The rejection states that the present claims further provide for a pharmaceutical composition comprising a compound of formula (Ib) (i.e., (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid) or a pharmaceutically acceptable salt thereof and

at least one other therapeutically active agent such as a PDEV inhibitor selected from sildenafil, verdenafil, taladafil, etc.

The rejection states that in particular, one skilled in the art could not practice the presently claimed subject matter of using the claimed compounds for the myriad of disclosed uses without undue experimentation because the artisan would have expected that the interaction of a compound with a particular receptor (i.e., in this case, the elected compound of (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid and salts thereof, and the alpha-2-delta receptor) would have been highly specific given what is known about receptor-drug interaction and, given the state of the art and the lack of any disclosure or guidance provided by Applicant supporting the idea that such a compound would, in fact, bind this same receptor. The rejection states the artisan would not have been imbued with a reasonable expectation of successfully using the claimed compound for any one or more of the disclosed uses.

The rejection refers to *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (Emphasis added.)

The rejection states that the instant claims are directed to the compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid, as well as the inclusion of such a compound into a pharmaceutical composition, along with one or more pharmaceutically acceptable excipients, diluents or carriers, into which may further be incorporated at least one other therapeutically active agent, such as a PDEV inhibitor, to be used for the treatment of various conditions, including epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, sleep disorders, osteoarthritis, rheumatoid arthritis, neuropathological disorders, visceral pain, functional bowel disorders (e.g., gastroesophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, inflammatory bowel diseases, such as Crohn's disease, ileitis, ulcerative colitis) and visceral pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis (p.7, Specification), which are conditions in which the alpha-2-delta receptor "is implicated" (p.9, Specification). The rejection states that the instant specification as originally filed lacks adequate guidance, direction or discussion to apprise

the skilled artisan how the claimed compound may be used to achieve the disclosed utilities for treating conditions wherein the alpha-2-delta receptor has been implicated, such as epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, sleep disorders, osteoarthritis, rheumatoid arthritis, neuropathological disorders, visceral pain, functional bowel disorders (e.g., gastroesophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, inflammatory bowel diseases, such as Crohn's disease, ileitis, ulcerative colitis) and visceral pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis (p.7. Specification), with at least a reasonable expectation of successfully achieving the treatment of the same. The rejection states that the instant specification fails to present any evidence, either in the form of data or scientifically sound reasoning, which would provide such a reasonable expectation that the claimed compounds would have been effective to treat the disclosed disorders. The rejection states that it is noted that Applicant need not necessarily demonstrate the precise manner in which the claimed therapeutic agent(s) ameliorate a particular disease state, such a mechanism must be elucidated in cases where Applicant relies upon a correlation between the particular activity of a compound (e.g., inhibition of a particular enzyme, binding to a particular receptor, etc.) and a reasonable expectation of efficacy in treating a particular disease.

The rejection states that in the instant case, Applicant relies upon the mechanism of action (i.e., interaction with the alpha-2-delta receptor) underlying the purported biological activity to establish that the genus of compounds instantly claimed would have been useful for treating conditions in which the alpha-2-delta receptor "is implicated". The rejection states that notably, however, the purported effect and/or specific interaction of the instantly claimed compound with the alpha-2-delta receptor is never described within the four corners of the instant specification. The rejection states that, in other words, though Applicant's inventive concept rests upon the correlation between the particular activity of the claimed compounds in interacting with the alpha-2-delta receptor to provide a reasonable expectation of efficacy in treating the disclosed disease(s) or disorder(s), the actual activity of the instantly claimed compound and the receptor with which it is proposed to interact is not adequately described in the accompanying specification so as to enable the full scope of the instant claims

The rejection also states that in order to be enabled to practice the present invention, the skilled artisan would have to accept on its face that the instantly claimed compound would have been more than capable of interacting with and binding the alpha-2-delta receptor such that the disclosed disease(s) or disorder(s) could actually be treated. The rejection states that given the state of the art at the time of the invention which clearly recognized the high degree of specificity required for drugs to interact with particular

receptors and, thus, the unpredictability with regard to the same, the instant specification would have been viewed as lacking an enabling disclosure as to how to use the instantly claimed compound for the various disclosed uses.

The rejection refers to Julien ("Chapter 2: Pharmacodynamics: How Drugs Act", *A Primer of Drug Action* (Ninth Edition); Worth Publishers, 2001:37-57) is cited. The rejection states that Julien teaches that, "As discussed, receptors exhibit high specificity both for one particular neurotransmitter and for certain drug molecules. Making only modest variations in the chemical structure of a drug may greatly alter the intensity of a receptor's response to it. For example, amphetamine and methamphetamine (Chapter 7) are both powerful psychostimulants. Although their chemical structures are very close, they differ by the simple addition of a methyl (-CH3) group to amphetamine, forming methamphetamine. Methamphetamine produces much greater behavioral stimulation at the same milligram dosage. Both drugs attach to the same receptors in the brain, but methamphetamine exerts a much more powerful action on them, at least on a milligram basis. The drug molecule with the "best fit" to the receptor (methamphetamine, in this example) elicits the greatest response from the cell. In pharmacologic terms, methamphetamine is more potent than amphetamine, because a lower absolute dosage achieves the same level of response as a higher dose of amphetamine. As a consequence of drug binding to a receptor, cellular function is altered, resulting in observable effects on physiological or psychological functioning. The total action of the drug in the body results from drug actions either (1) on one specific type of receptor or (2) at multiple different types of receptors." (p. 48-49)

The rejection states that given that the art expressly acknowledges the unpredictability of receptor-drug binding in that the interaction is highly specific and that seemingly simple or uncomplicated modifications to a compound result in drastically different levels of pharmacologic activity, one of ordinary skill in the art at the time of the invention would not have accepted on its face Applicant's statement that the instantly claimed compound(s) could be used to bind to the alpha-2-delta receptor and treat the various disclosed disorder(s) and/or disease(s) with a reasonable expectation of success, absent any direction, evidence or guidance to this effect. The rejection also states that in light of such, the artisan would have required sufficient direction as to how the instantly claimed compound(s) could actually be used to treat such disease(s) and/or disorder(s) by elucidating its ability to bind to the alpha-2-delta receptor with at least a reasonable expectation of success. The rejection also states that such success would not have been reasonably expected given that receptors have highly specific binding sites that are only capable of interacting with certain drug molecules and the idea that any drug could bind any receptor is not an outcome that would have been reasonably expected by one of ordinary skill in the art in view of the state of the art and Applicant has failed to provide any guidance

supporting the assertion that the instantly claimed compound(s) are, in fact, capable of binding the alpha-2-delta receptor. The rejection states that absent this disclosure, the present specification fails to enable the full scope of this invention as it related to the objective of using the instantly claimed compounds for the myriad of disclosed uses in the instant specification and, thus, fails to rebut the presumption of unpredictability in the art with regard to this same objective.

The rejection refers to MPEP at §2164.08.

"All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involved the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation."

The rejection states that Applicant provides various compounds and methods of synthesizing each, wherein Example 10 provides a method of synthesizing the instantly claimed compound, (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid, as well as numerous exemplary pharmaceutical formulations that comprise an active ingredient of the claimed compounds of the invention. The rejection states that although Applicant's examples in this regard are duly noted, Applicant has failed to demonstrate that the instantly claimed compound [i.e., (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid] actually functions to achieve the disclosed therapeutic use of interacting with the alpha-2-delta receptor such that one of skill in the art would have thereby recognized its efficacious use in treating any one or more of the disclosed disease states. The rejection states that the specification fails to present either a working or prophetic example(s) or a clear, scientifically sound explanation as to what, in fact, enables the interaction with the alpha-2-delta receptor such that the skilled artisan would have been imbued with at least a reasonable expectation of predictability of action in using the instantly claimed compound for use in treating any one or more of the disorders disclosed as being responsive to such an effect. The rejection states that absent such guidance, the experimentation required to determine if there is any activity of any of the compounds in treating the disclosed disorders, and further, to determine, without needing to resort to random speculation, what therapeutic amounts would be available to even start testing for a therapeutic effect, would clearly be undue. The rejection states that further, it is noted that, while the lack of a working embodiment cannot be the *sole* factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable

nature of the chemical and pharmaceutical arts and the limited direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

The rejection also states that although the instant specification states that the instantly claimed genus of compounds, which encompasses the specifically elected compound [i.e., (2S,4S)-4-(3-fluorobenzyl)-pyrtolidine-2-carboxylic acid], interact in some (unspecified) manner with the alpha-2-delta receptor to treat disorders in which the alpha-2-delta receptor "is implicated", the disclosure fails to provide any mechanistic discussion or provide any evidence or data, preclinical or otherwise, supporting the concept that the instantly claimed compound would, in fact, be effective to interact in such a way with the alpha-2-delta receptor so as to achieve the therapeutic treatment of the disclosed disorders. In the absence of such discussion or evidence, it is clear that the instant specification fails to support the enablement of the instantly claimed compounds in functioning to interact with the alpha-2-delta receptor such that the skilled artisan would have reasonably expected that the instantly claimed compound, effective in this manner, would have functioned to achieve the disclosed utility for treating conditions in which the alpha-2-delta receptor "is implicated" in a subject in need thereof.

The rejection states that as stated in MPEP §2164.04[R-1], "Doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation." The rejection states that in the instant case, the information that is missing is a clear correlation between the claimed compound and its efficacy in treating the disclosed conditions, either through specific evidence in the form of data demonstrating such a fact or at least a sound mechanistic correlation between the claimed compound, *its ability to function in such a manner* and the amenability of the claimed disease state to treatment using an agent capable of functioning in this manner. The rejection states that although one of skill in the art might very well known how to treat a patient with the claimed compound once a diagnosis had been made of the claimed disorder (e.g., epilepsy, hypokinesia, etc.), it remains that the instant specification conspicuously fails to provide any guidance or direction in support of the *reasonable expectation of success* in actually effecting the treatment of the disclosed disorders using the instantly claimed compound in the absence of any evidence supporting the allegation that the claimed compound is, in fact, effective to achieve such a therapeutic objective, either by reduction to practice or at least by elucidating the mechanism by which the claimed compound works and correlating such activity to therapeutic improvement of the disclosed disorders or diseases. The rejection states that in the absence of this information, the specification fails to provide adequate guidance and/or direction to one of skill in the art at the time of the invention that would have enabled such a

person to practice the instantly claimed invention without having to resort to undue experimentation to determine how, in fact, one would achieve the instantly disclosed therapeutic objective(s).

The rejection states that the basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice the full scope of the invention would be *undue*. The rejection refers to *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (Emphasis added.) The rejection states that accordingly, in the absence of any adequate disclosure, direction or guidance as to how one would go about using the instantly claimed compound with a reasonable expectation of successfully treating the disclosed disorder(s), it remains that the pharmaceutical, chemical and medical arts are notoriously complex such that methods of use would have been sufficiently unpredictable to warrant the need for undue experimentation to actually practice the full scope of the invention as instantly claimed.

The rejection states that in view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor or scientist with several years of experience in the art.

The rejection states that as the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation or ability to make and use the full scope of the invention as instantly claimed, given the disclosure and supporting examples provided in the present specification and the state of the art at the time of the invention. The rejection also states that in order to actually achieve the claimed invention, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the embodiments presently claimed.

Applicant traverses the 35 U.S.C. §112, first paragraph, rejection of the claims and respectfully requests that the Examiner withdraw the rejection and allow the claims (as amended).

As an initial note Applicant submits that the instant claims are drawn to compounds and pharmaceutical compositions. Accordingly, the claims only need to be enabled for a single utility. Nor are Applicant's claims limited to the treatment of a particular species e.g.,

humans. In contrast, Applicant notes that the rejection refers to a plethora of utilities and impliedly relates to the treatment of humans.

It is well settled law that the burden is on the Examiner to provide evidence why assertions of utility should not be accepted. In the instant case the Examiner has merely made conclusory statements without sufficient supporting evidence why Applicant's assertions of activity should not be accepted as true. Without such supporting information, the rejection of the specification/claims under 35 U.S.C. §112 first paragraph for lack of enablement is contrary to well established law. Ex parte Kenaga, 189 USPQ 61, 64 (P.T.O. Bd. App. 1974), quoting In re Marzocchi, 169 USPQ 367 at 370:

> "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back assertions of its own with acceptable evidence or reasoning which is in consistent with the contested statement."
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> The C.C.P.A. held in In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971),
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> "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

Id. at 369. The burden is on the Examiner to come forth with evidence to establish a prima facie case. No persuasive factual evidence has been presented to establish a prima facie case pertaining to §112, first paragraph. Therefore, the statements in the present application must be taken as the truth. In re Langor, supra at 297; In re Marzocchi, supra at 369. Thus, Applicants request that the §112 rejection be withdrawn.

This issue has been revisited in In re Brana 34 U.S.P.Q.2d 1437 (CAFC 1995). The court quotes the above quotation from In re Marzocchi and concludes;

> "From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Id. at 224, 169 U.S.P.Q. at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility."

In re Brana 34 U.S.P.Q.2d 1437, 1441 (CAFC 1995).

While the new rejection is lengthy, and its text differs somewhat from the earlier rejection, Applicants submit that the instant rejection repeats the conclusory nature of the previous rejection. Essentially the rejection states that Applicants have not provided any activity data for their compounds. Yet the rejection again fails to provide any evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. This clearly is not sufficient to shift the burden under the standard enunciated by the CAFC.

Applicants also note that the rejection has not stated that the Applicants asserted treatment of certain diseases e.g., pain is an "incredible utility". Thus, Applicants assertions of utility should be acknowledged absent sufficient specific evidence such as mandated by the above caselaw.

The main difference in the instant rejection in comparison to the previous rejection is the inclusion of a reference Julien ("Chapter 2: Pharmacodynamics: How Drugs Act", *A Primer of Drug Action* (Ninth Edition); Worth Publishers, 2001:37-57) with the suggestion that this reference is sufficient evidence to shift the burden to Applicants to provide activity data. The rejection broadly refers to the publication and pharmaceutical research in general stating the "unpredictability of receptor-drug binding in that the interaction is highly specific and that seemingly simple or uncomplicated modifications to a compound result in drastically different levels of pharmacologic activity". First, this is a conclusory general statement that, implicitly, if not explicitly, requires pharmaceutical data for all pharmaceutical compound claims. Yet this is simply not the standard by which enablement is judged as is clearly evident from, for example, the cited caselaw and the thousands of pharmaceutical compound patents granted by the United States Patent Office. The above textbook does not "provide[s] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility". Clearly any such evidence must be more specific and relate to the instant claims. Second, even the general statement supports Applicant's position since it states "simple or uncomplicated modifications to a compound result in drastically different levels of pharmacological activity." Applicant submits that even "drastically different levels of pharmacological activity" support enablement as there is some level of activity.

In addition, the specific example referred to in the rejection (Chapter 7) relating to the psychostimulants amphetamine and methamphetamine also does not shift the burden to Applicants. In fact it supports Applicant's claims. The rejection admits that both compounds while differing in structure are active. Applicant submits that some level of activity is sufficient evidence of utility. Again, the example simply does not support the rejection since the rejection admits that both amphetamine and methamphetamine are active-they just have different activity levels. Applicants strongly reject the implied notion that to be enabled compounds must have the "same" level of activity. Clearly Applicant's compounds can have varying levels of activity and Applicant has not asserted otherwise. In addition, amphetamine and methamphetamine are not alpha-2-ligands—they are part of a group of compounds that act by increasing levels of for example, serotonin on receptors other than alpha-2-ligands.

In compliance with 112 Applicant asserts that his claims are enabled as amply supported in the specification. First, it is well known that alpha-2-delta ligands are associated with pharmacological activity as stated in the instant specification paragraphs [0003] to [0006].

Second, Applicant submits that in compliance with the above-described case law he has stated that the compounds are effective for their intended use in the specification (e.g., see the instant U.S. published application paragraph [0116]; and paragraphs [0118] through [0131].

Applicant submits that he has fully enabled the use of the instantly claimed compounds. The instant U.S. published application in paragraphs [0207] and [0209], describe appropriate dosage levels. Treatment methods are disclosed in the paragraphs [0172]; [0186]; [0189]; [0196]; [0199]; [0201]; [0205]. The specification teaches at paragraphs [0207] and [0208] appropriate dosage levels. Further, the specification teaches (see U.S. published application paragraph [0116]) test protocols which aid in determining the activity/relative activity of the compounds and thus appropriate dosage levels. In addition, the specification is replete with description of how to formulate the compounds. Applicant submits that this is sufficient to meet the standards of enablement under 35 U.S.C. §112.

The points and concerns raised by the Examiner having been fully addressed. Applicants urge that this application is in condition for allowance, which action is respectfully requested.

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445.

Respectfully submitted,

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